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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,183	11/14/2001	Alan Gewirtz	43826-9	6995

7590 09/05/2006

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,183	GEWIRTZ, ALAN	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-9,11 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,11 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 April 2006 has been entered.

Applicant's response filed 28 April 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 29 December 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Kreutzer et al. (WO 00/44895, or record).

At the outset it is noted that the instantly rejected claims are not considered to benefit from the priority date of the provisional application, i.e. that of 60/248,346. This is because said provisional application does not teach "small interfering RNA guide sequences" as instantly claimed. Should applicants disagree, applicants are requested to point out with particularly by page and line number where support in the provisional application for this limitation exists.

It is further noted that the declaration submitted under 37 CFR 1.131 effectively antedates Kreutzer reference as it relates to claims 1, 2, 5, 7, 8, 9, and 11, since the priority date accorded these claims of 14 November 2000 is less than one year from the publication date of the Kreutzer reference, and since said declaration properly shows reduction to practice of the instantly claimed invention prior to 3 August 2000, the publication date of the Kreutzer reference. However, due to the aforementioned denial of priority for claims 22-27, Kreutzer et al. is more properly applied under 35 U.S.C. § 102(b), since it is considered to teach all the limitations of claims 22, and 24-27 as discussed below.

Claim 22 is drawn to a method for disrupting a mammalian target gene in vitro, comprising administering a small interfering RNA guide sequence which is homologous to a target gene to induce RNAi. The dependent claims further recite wherein the cells reside in a population of melanoma, leukemia, tumor, or transformed cells, or wherein said cells are malignant, or wherein the interfering RNA is formulated as part of a pharmaceutical formulation, or wherein the dsRNA targets a human disease or disorder.

Kreutzer et al. teaches a method for disrupting a mammalian target gene in vitro, comprising administering a small double stranded RNA sequence which is homologous to a target gene to induce RNAi, wherein such methods are recited as targeting oncogenes, which is

considered to inherently teach targeting cells that reside in a melanoma, leukemia, tumor, or transformed cells population, and wherein said cells are malignant, and wherein the interfering RNA is formulated as part of a pharmaceutical formulation, or wherein the dsRNA targets a human disease or disorder.

Applicants have argued that the Kreutzer reference fails to "provide evidence of" each and every element of applicants claimed invention, and therefore fails to provide anticipation. This assertion is based on the fact that Kreutzer exemplifies his invention in a mouse cell line, and prophetically teaches its use in human cell lines, whereas applicants have exemplified their invention in a human cell line. It is applicant's contention that "Mice are not simple small people", and it is suggested that applicants exemplification in a human cell line cannot be anticipated by a similar exemplification in a mouse cell line combined with a prophetic teaching that such methods could be performed in human cell lines.

In response, it is noted that there is no apparent dispute as to whether Kreutzer et al. teaches all the limitations of applicants rejected claims, because indeed Kreutzer et al. do teach all such limitations. It is also important to point out that applicants are using the wrong standard for anticipation. Applicants apparent standard is that a reference must "provide evidence of each and every element of applicants claimed invention" (applicants arguments page 13, emphasis supplied) in order for a reference to be anticipating. Of course, as applicant's representative is no doubt well aware, a reference may also merely *teach* each and every element of applicants claimed invention and still be anticipating. Applicants have provided no citation for their heightened standard of anticipation, nor is the examiner aware of one, and arguments directed to this heightened standard are therefore unconvincing.

In an attempt to respond to applicant's arguments, it is presumed that applicant's apparent contention is that that mouse cell lines are not representative models of human cell lines, and that the reference of Kreutzer et al. is not enabled therefore. For example, applicants have noted at page 13 that "mouse models have often failed to accurately reproduce the initiation of many sporadic human tumors" and that "many have questioned how faithful is the mimicry of human diseases in mice." Further, "as a result, human cells have adapted certain intrinsic mechanisms that are not found in mice -- and created differences between the cellular responses in the two species."

This line of argumentation is not considered convincing. While it is acknowledged that mice are not identical to humans, one of ordinary skill in the art would nevertheless recognize that mice are generally representative of humans in the absence of specific evidence to the contrary. Further, it is noted that there is no manipulative difference in the exemplified steps performed by Kreutzer et al. as compared to those of applicants instant exemplified steps. Although applicants speculate extensively on differences between mouse cells and human cells, and how RNAi could possibly differ between the two, there is no evidence presented beyond a general reference supporting the generic notion that mice and humans are not identical. The reference does not mention RNAi, let alone describe any differences there between. Applicants arguments that RNAi would differ in mechanism between mouse cells and human cells is merely unsupported speculation. As applicants are also no doubt aware, arguments may not take the place of evidence. Since the manipulations are identical, and since no evidence exists that the mechanisms of RNAi would differ between mice in human cell lines, these arguments are not convincing.

Applicants also argue that Kreutzer demonstrates the silencing of an exogenous, non-mammalian gene. Applicants state that "One of ordinary skill in the art would recognize that the use of an artificial marker gene is often done to make it 'easier' to achieve and visualize gene silencing. It is much more difficult to obtain dsRNA silencing of the targeted mammalian gene." While it is agreed that artificial marker genes make it easier to visualize gene silencing, there is absolutely no evidence that it is "easier" to achieve inhibition of an exogenous gene, nor is there any evidence that it is much more difficult to obtain dsRNA silencing of the targeted mammalian gene. Given applicants statement that one of ordinary skill would recognize that it is easier to achieve target knockdown, perhaps a reference to this effect would support the otherwise mere assertion that inhibition of introduced genes is somehow easier. To the contrary, as pointed out by Phillip Sharp (Genes and Dev. 1999, 13:139-141), RNAi has been shown to work on specific genes in many organisms and concludes "the RNAi phenomenon is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes." Applicants assertion that it is much more difficult to obtain dsRNA silencing of a targeted mammalian gene appears to have no scientific basis. As one of ordinary skill in the art knows, the specificity for a target gene that confers the ability to distinguish between an endogenous or exogenous gene is provided solely by the introduced dsRNA. Thus, should one wish to silence an exogenous gene, one would develop a dsRNA that corresponds to the exogenous gene. Should one wish to silence an endogenous gene one would merely develop a dsRNA that corresponds to the endogenous gene. Applicant have not pointed to, nor is the examiner aware of, any evidence that the RNAi mechanism itself distinguishes at all between endogenous or exogenous genes.

Finally, applicant's argue that Kreutzer describes a region I, and a region II which are auto complementary, which therefore runs contrary to applicants invention whereby transcription of each [RNA] is independently controlled to generate paired RNAs. This characterization is incomplete, since on page 4 at line 29 of the 35 USC 371 filing of Kreutzer et al. (U.S. Application Number 09/889,802, which is a certified translation of the instantly cited Kreutzer WO document), Kreutzer clearly states that "the double stranded structure is formed by two separate RNA single strands or by auto complementary regions". Accordingly, Kreutzer et al. is considered to teach the above limitation whereby transcription of each [RNA] is independently controlled to generate paired RNAs. The rejection is maintained therefore.

Claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (U.S. Patent 6,506,559, of record) for the same reasons of record as set forth in the Office Action mailed 5/23/05.

Applicants have traversed the instant rejection in much the same way that the rejection over Kreutzer et al. was traversed. The general theme of applicants arguments can be summarized by the notion that since Fire et al. did not exemplify but merely prophetically states that such methods could be carried out in humans, that Fire et al. could not anticipate the instant claims, which require inhibition in humans. In support of this argument, applicant states that "Fire teaches RNAi operations only in an embryonic nematode invertebrates cell from *C. elegans,*" and that the examiner improperly and "erroneously credited the Fire patent with far greater breadth than could possibly have been enabled by the limited teachings that were

provided by the disruption of targeted gene expression that was demonstrated only in embryonic in vertebrate cells."

In response, it is noted that applicants arguments repeatedly confuse the issue of what is taught versus what is exemplified. It is acknowledged that Fire does not exemplify RNAi in human cells; however, Fire clearly *teaches* such inhibition throughout the issued patent. This mistake is repeated throughout applicants arguments.

Again, this is considered to form an improperly high and unfounded bar for anticipation. As above, it is presumed that applicants are intending to argue that Fire et al. is not enabled for RNAi mediated inhibition of gene expression in human cells. Again, it is reiterated that there are no manipulative differences between the methods disclosed by Fire et al. and those disclosed instantly. In other words, there are no manipulative steps taken by applicant that Fire didn't do that serves to enable the instant invention. While it is acknowledged that a different structure (i.e. a different cell type) was used, this is not considered a manipulative difference. If Fire had used human cells in his own method, the evidence indicates that RNAi mediated inhibition would have been achieved, particularly since as cited above, Sharp (id) teaches that "the RNAi phenomenon is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes."

Applicants have pointed to some publications that are alleged to indicate that Fire himself believed that his claimed method would not work in a human cell. While applicants have provided citations in support, no reference has been supplied either as an exhibit or in an IDS that could be considered by the examiner and arguments directed cannot be considered accordingly. Nor have any quotes been provided. Applicants have also pointed to statements

from Kreutzer et al. regarding a "general perception in the art... that RNAi cannot be made to work in mammals. It was believed that protocols used for in vertebrate and plant systems would not be affected in mammals due to the interferon response, which leads to an overall block to translation and the onset of apoptosis..." It is important to understand that these comments some from a competitor of Fire et al., in a patent application, which therefore does not carry the same weight as if they appeared in a peer-reviewed journal article.

Applicants refer to the list of organisms in Fire against which his method is disclosed as working in as wishful thinking, and further characterize the examiner's arguments as being supported by wishful thinking in regards to the enablement of Fire as prior art against the instantly claimed invention. Applicants take great care to characterize the examiner's arguments as bringing up a discussion of whether or not Fire is enabled, and use this characterization to justify a lengthy discussion that attempts to undermine the enablement of the issued Fire patent. Applicant contends that the examiner did this because "he recognizes that the Fire patent lacks enablement to support the arguments being made." (Applicants arguments page 18). Applicants characterization is based on the fact that the examiner indicated that substantial additional experimentation might be required to practice the invention of Fire in human cells, but that this is not the same as undue experimentation. Applicants feel that they are "left with no alternative but to be responsive and discuss enablement of Fire, rather than anticipation under 35 U.S.C. § 102(e)." (Applicants arguments page 19).

In undermining the enablement of Fire et al. applicants state that "nowhere do the facts suggest that the amount of direction or guidance presented by Fire, which is limited to a biological response of a simple embryonic nematode cell, could or would be translated by one of

ordinary skill in the art to sufficient knowledge to practice the invention in a human cell". This inappropriately shifts the burden of proving enablement to the already issued patent, which is presumed to be enabled, and applicants arguments are unconvincing therefore. Applicants state that "not even Fire believed that his invention was enabling for cells other than the exemplified nematode invertebrate cells." (Applicants arguments page 20). Applicants generally assert from this that "far more than routine procedures would be necessary for one of ordinary skill in the art to adapt procedures taught by Fire to the instant invention."

In doing so, applicants are clearly denigrating the validity of claimed subject matter belonging to Fire et al., since Fire et al. has patented claims directed to the instant invention in animal cells, and since applicants assert that Fire is enabled only for RNAi in C. elegans. Leaving aside the entire issue of propriety in casting aspersion on issued patents, applicants arguments are notably light on detail and heavy on argument when it comes to undermining the enablement of Fire. It is noted and acknowledged that Fire did not exemplify his invention in human cells. It is not necessary to do so in order to anticipate applicants claimed invention, because the prior art is presumed to be enabled, and nothing since his invention shows that undue experimentation would have been required to enable it. To the contrary, the field is rife with investigators furthering the ideas set forth in the Fire patent. The scope granted Fire was pioneering, as he was the recognized inventor of the RNAi process, and is not required to provide exemplification for all forms of his invention as he envisioned it.

Applicant's representative repeatedly attempts to delve into the belief system of Fire et al. in a manner that is somewhat baffling, and certainly unsupported. Applicants only "support" for Fire's views come from two citations, that are otherwise unaccompanied by the actual articles,

nor even any quotations therefrom. Thus, we have no record on which to evaluate Fire's personal opinion of his otherwise patented invention. Even if such evidence of Fire's mindset were actually presented, this would not be sufficient, since the objective evidence must indicate undue experimentation to prove Fire inoperable. Mere speculation to the contrary, even from the inventor, in the absence of supportive evidence, is not considered sufficient to consider the presumably valid claims of Fire to be not enabled. Arguments presumption of insight on Fire's beliefs relating to RNAi are therefore unconvincing. As repeated above, nothing in the instant application expands upon the teachings of Fire et al., which is presumed to be valid, particularly since literally thousands of post filing references have shown his invention to work.

Finally the examiner was correct in arguing that unexpected results are not considered in an anticipation rejection. There is no guidance the examiner is aware of, nor have applicants pointed to, whereby unexpected results may be considered in rejections made under 35 USC 102. If applicant's representative is aware of such guidance, it is requested that it be cited and provided by page and line number. The rejection is maintained therefore.

Claim Rejections - 35 USC § 103

Claims 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. as applied to claims 1, 2, 5, 7-9, 11, 21-22 above, and further in view of Gewirtz et al (WO 92/19252) Kreutzer et al. (cited above), and Sharp (Genes and Dev. 1999, 13:139-141, cited above).

Applicant's arguments with respect to the previous rejection under 35 U.S.C. § 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Claims 22 and 23 are drawn to a method for disrupting target gene expression *in vitro* in a human cell comprising providing small interfering RNA guide sequences which are homologous to a portion of a target gene wherein the target gene is c-Kit. Additional dependent claims 24-27 require that the human cells are particular types cells, are malignant, that the interfering RNA comprises part of a pharmaceutical composition and that the pharmaceutical composition is used to treat human disease or disorders.

Fire et al. teach a method for inhibiting expression of a target gene using double stranded RNA to induce RNAi in a cell *in vitro* (Column 26, claim 1) wherein the cell is from an animal (Column 26, claim 6) and the dsRNA has a length of identical nucleotide sequences that may be at least 25, thereby teaching short interfering RNA guide sequences (col. 8, line 5). Fire et al. teach that the cell with the target gene may be derived from or contained in any organism (column 8, line 13-14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55) and that "the present invention could be used for treatment or development of treatments for cancers of any type, including solid tumors, sarcomas and leukemias..." (Column 10, lines 26-28). Fire et al. teach target genes that are oncogenes (col. 11). Fire et al. teach that lipid mediated carrier transport can be used to introduce nucleic acids to cells (Column 9, lines 55-60). Fire et al. also teach that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein). Fire et al. teach that using the methods of their invention, gene disruptions may be used to discover the function of a target gene and to produce disease

models in which the target gene is involved in causing or preventing a pathological condition (col. 5, lines 30-37). Fire et al. disclose, that relative to antisense approaches, their invention has advantages in the stability of the material to be delivered (col. 3, line 20). Fire et al. do not teach the nucleotide sequence of the oncogene c-Kit.

Gewirtz et al. teach the antisense inhibition of c-Kit proto-oncogene expression in human cells and that c-kit antisense oligonucleotides are particularly useful against leukemia (Abstract; pg. 15.). Gewirtz et al. disclose that the c-Kit cDNA sequence was known in 1987 and cite Yarden et al.

Kreutzer et al. teaches a method for disrupting a mammalian target gene in vitro, comprising administering a small double stranded RNA sequence which is homologous to a target gene to induce RNAi, wherein such methods are recited as targeting oncogenes, which is considered to inherently teach targeting cells that reside in a melanoma, leukemia, tumor, or transformed cells population, and wherein said cells are malignant, and wherein the interfering RNA is formulated as part of a pharmaceutical formulation, or wherein the dsRNA targets a human disease or disorder.

Sharp is added as a general reference supporting the idea that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to substitute an siRNA oligonucleotide in place of the antisense oligonucleotide in a method of inhibiting the expression of the oncogene c-Kit *in vitro* using an antisense inhibitor in human leukemia cells (as taught by Gewirtz et al.), wherein the dsRNA

was comprised in pharmaceutical composition (as taught by Fire or Kreutzer) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because dsRNA can be used to initiate RNA interference *in vitro* by targeting oncogenes in human cells including leukemias (as taught by Fire and Kreutzer) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire and Kreutzer).

One of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz et al.) using a 25 bp double stranded RNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire and Kreutzer) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire and Kreutzer).

One of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz et al.) using a 25 bp double stranded RNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire and Kreutzer) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because Fire et al. teach that dsRNA can be used to initiate RNA interference in human cells and because relative to antisense approaches,

dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire and Kreutzer). Sharp further supports the fact that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. D. Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JDS

JAMES SCHULTZ, PH.D
PRIMARY EXAMINER